Remarks

In view of the foregoing amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

This submission is accompanied by a petition for three-month extension of time. The $1110 fee for this extension should be charged to deposit account 14-1138. Any additional fees should be charged or overpayment credited to this same account.

Claims 1-9 and 11-32 have been cancelled without prejudice. Claim 10 has been amended and new claims 33-35 have been introduced.

Support for the requirement that the condition for treatment or prevention is renal fibrosis occasioned by diabetes is found, *inter alia*, in previously presented claim 16. Support for the requirement that the means for modulating CDA activity is an AT1 receptor antagonist administered in an effective amount appears, *inter alia*, on page 15, line 13. With respect to the requirement that the expression or activity of CDA1 is reduced, support can be found on page 6, line 11 of the specification. Support for the requirement that a result of the method is a decrease in expression of an extracellular matrix protein in the kidney is found, *inter alia*, on page 12, lines 30-33. New claim 33 finds descriptive support at page 15, lines 11-13 and Figure 3. New claim 34 finds descriptive support at page 5, lines 28-30 and the Examples. New claim 35 specifies that the administering of the AT1 receptor antagonist is carried out for treating "CDA1 modulated renal fibrosis resulting from diabetes". Therefore, no new matter has been added by the way of these amendments.

Claims 10 and 33-35 remain pending. No excess claim fees are due with this submission.

The objection to claim 10 is overcome by the above amendments. Claim 10 now recites cell division autoantigen-1 (CDA1) in place of the abbreviation "CDA". This objection should be withdrawn.

The rejection of claims 10-16 and 21 under 35 U.S.C. § 112 (2nd para) for indefiniteness is overcome by the above amendments. Claim 10 expressly recites the step of "administering to a subject in need thereof a therapeutically or prophylactically effective amount of an AT1 receptor antagonist…." No steps required for practice of the method are omitted. Therefore, this basis of rejection should be withdrawn.

The rejection of claims 10-16 and 21 under 35 U.S.C. § 112 (1st para) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

Claim 10 has been limited to the treatment or prevention of "cell division autoantigen-1 (CDA1) modulated renal fibrosis, the fibrosis resulting from diabetes." It is respectfully submitted that ample enablement for treatment of prevention of this condition is provided in the specification.

The specification demonstrates a clear correlation between the level of CDA1 in kidney cells and the secretion of extracellular matrix proteins. Figure 2 demonstrates the upregulation of CDA1 expression in podocytes in a well accepted animal model of diabetes. Furthermore, Figure 6 demonstrates that expression of CDA1 in renal tubules and the interstitium is increased over a period of at least 32 weeks in a rat diabetic model.

In establishing a causal connection between the increase in CDA1 expression and fibrosis, the applicants have also demonstrated a concomitant increase in the expression of extracellular matrix proteins such as fibronectin and collagen IV (*see* Figures 4A to 4D). Given that it was well accepted at the priority date that fibrosis is caused by the excessive secretion of extracellular matrix proteins, persons of skill in the art would have expected from this data that fibrosis could be treated or prevented by decreasing the expression of extracellular matrix proteins in the kidney of a subject.

It will be appreciated that fibrosis could logically be prevented by maintaining low levels of CDA1 in a cell, given that low levels of CDA1 will result in the decreased expression of extracellular matrix proteins. Similarly, an existing fibrosis could be prevented from advancing to a more serious condition by limiting the expression of CDA1.

It will be further appreciated that an existing fibrosis may be reversed by the present invention. The level of extracellular matrix protein in a tissue is controlled by the rate of synthesis of the protein offset by the rate of degradation. Extracellular matrix proteins will naturally degrade over time. In many instances the degradation is actively progressed by the action of various proteases resident in the interstitial space. Thus, where the level of CDA1 is maintained at a low level, the rate of protein degradation can be greater that the rate of synthesis thereby leading to a net decline in the level of extracellular protein.

At page 15, lines 11-13, it is recited that the treatment with an AT1 receptor antagonist, specifically valsartan, prevented increased CDA1 expression following angiotensin II infusion (which otherwise would induce CDA1 expression). Thus, the present

application fully enables a person of skill in the art to practice the presently claimed invention.

The United States Patent and Trademark Office ("PTO") has questioned enablement of the step of "modulating the expression and/or activity of a CDA". Without accepting the correctness of the objection, but to facilitate prosecution of this application, claim 10 has been amended to recite the step of "administering … a therapeutically or prophylactically effective amount of an AT1 receptor antagonist," which "reduces the expression or activity of CDA1 in a kidney cell of the subject…". This is fully supported by the specification, as noted above, and overcomes this basis of rejection.

Moreover, the PTO should appreciate that AT1 antagonists are a well-defined and well-known class of therapeutics, many of which were registered therapeutics and in clinical use at the priority date (albeit for different therapeutic utility, namely the control of hypertension). Accordingly, persons of skill in the art would immediately be familiar with a range of suitable compounds. Further, the person of skill in the art would be familiar with the clinical use of these agents in respect of hypertension and would at once be guided by the established dosage regimes for that clinical indication, and could have practiced the invention without anything more than routine experimentation.

It was known that these agents effectively antagonized the AT1 receptor, and based on the data presented in the present application, persons of skill in the art would have expected AT1 receptor antagonists to be suitable for treating or preventing "cell division autoantigen-1 (CDA1) modulated renal fibrosis, the fibrosis resulting from diabetes" as presently claimed. The soundness of this expectation is grounded on the applicant's discovery of functional linkages between the AT1 receptor, the CDA1 molecule, and the development of renal fibrosis.

In support of applicants' position, submitted herewith are a Declaration of Zhonglin Chai, Ph.D. under 37 C.F.R. § 1.132 (hereinafter "Chai Decl.") and a Declaration of Mark Emmanuel Cooper M.B., B.S., Ph.D. under 37 C.F.R. § 1.132 (hereinafter "Cooper Decl.").

As explained by Dr. Chai, persons of skill in the art would have been fully aware of and able to adopt the dosage protocols of any clinically available AT1 receptor antagonist as used in the treatment of hypertension. *See* Chai Decl. ¶¶ 7-13 (and Exhibit A thereto). The soundness of applicant's position is confirmed by Dr. Cooper, who was working in the field of diabetes research and clinical practice at the priority date. Cooper Decl. ¶¶ 1-3.

The PTO further alleges at page 5 of the office action that the term "CDA1" is no more than an arbitrary name. The applicants respectfully disagree on the basis that all nomenclature for biological molecules is arbitrary. Put simply, a research scientist identifies a new molecule and must give that molecule a name of some type. Often the name will have regard to a biological or physical characteristic, but that does not change the fundamentally arbitrary nature of the name. As is often the case in the biological sciences, a molecule is discovered by two different parties and accorded different (arbitrary) names by the respective parties. At some later point in time it becomes apparent that the two names refer to the same molecule (as is the case with CDA1 and DENTT), however, that is not to say that the skilled person can not ascribe a clear meaning to the terms CDA1 and DENTT. Indeed, the present specification clarifies that CDA1 and DENTT are indeed the same molecule (*see* page 8, lines 28 to 30). The overriding question must be whether or not the skilled person can ascribe a clear meaning to the term "CDA1", irrespective of the presence or absence of any alternative names for the molecule.

Putting to one side the existence of alternative names for CDA1, applicants submit that the term "CDA1" is clear to the skilled person at first instance. However, if any question remained at the time of filing, the specification provides many means for identifying a CDA1 molecule. Importantly, the description provides both nucleotide and protein sequence information (*see* Figures 7 and 8). Furthermore, on page 8 of the specification, a very detailed description of CDA1 is provided, including a reference to published patent application WO 02/36768. The CDA1 described in that document was identified from a human testis λgt11 cDNA library, and sequenced. The CDA1 is further characterized in the present specification in terms of sequence (Figures 7 and 8), molecular weight (79,430 Da), and isoelectric point (4.26). Structural characterization of the protein is also provided on page 8, lines 9-17. In addition to the foregoing, the specification (on page 8, lines 19-26) discloses changes in expression levels of CDA1 during the cell cycle. The skilled person would immediately understand that no restriction to the species of CDA1 is intended, and the claimed invention encompasses the CDA1 modulated fibrosis in both human and non-human animals.

For all the above reasons, applicants submit that the presently claimed invention is fully enabled by the specification. Therefore, the rejection of claim 10-16 and 21 for lack of enablement should be withdrawn.

The rejection of claims 10-16 and 21 under 35 U.S.C. § 112 (1st para) for lack of written descriptive support is respectfully traversed in view of the above amendments and the following remarks.

As noted above, a clear basis is provided in the specification for the involvement of CDA1 in increased extracellular matrix formation in renal fibrosis resulting from diabetes, as well as the ability of AT1 receptor antagonists to prevent increased CDA1 expression.

It is the burden of the patent office to demonstrate that the disclosed species of CDA1 is not representative of all CDA1. This the PTO has not done, presumably because the protein *is* well conserved among mammals and, therefore, adequately represents the claimed genus. Instead, the PTO has merely asserted that SEQ ID NO: 2 is not representative of all CDA1, without providing any evidence of that. Attached as Exhibit 1 is a Clustal alignment of seven mammalian CDA1 homologs obtained from a Blast search of Genbank using the human sequence. The Clustal alignment, performed on default settings, demonstrates a high degree of identity among the mammalian CDA1 homologs, namely between 68-93 percent identity with the human sequence. Therefore, the human CDA1 sequence described is the specification adequately represents the genus of CDA1.

For all of the above reasons, the rejection of claims 10-16 and 21 under 35 U.S.C. § 112 (1st para) for lack of written descriptive support is improper and should be withdrawn.

The rejection of claims 10-16 and 21 under 35 U.S.C. § 102(b) for anticipation by U.S. Patent No. 6,211,217 to Spinale et al. ("Spinale") is respectfully traversed.

A significant difference between the method disclosed by Spinale and the presently claimed invention is that the fibrosis treated by the methods disclosed in Spinale is caused by a surgical injury. In contrast, the presently claimed invention relates to kidney fibrosis resulting from diabetes. The significance of this distinction is supported by the accompanying Chai Decl. at ¶¶ 13-14.

The skilled person would appreciate that fibrosis operates by many different mechanisms. Indeed, the Background section of Spinale states:

> In most cases, fibrosis is a reactive process, and several different factors can apparently modulate the pathways leading to tissue fibrosis. Such factors include the early inflammatory responses, local increase in fibroblast cell populations, modulation of the synthetic function of

fibroblasts, and altered regulation of the biosynthesis and degradation of collagen.

Column 1, lines 33 to 39.

Given the many different mechanisms by which a fibrotic condition may be established in a tissue, and the many different combinations and interactions of effector molecules comprising those mechanisms, it is improper to assume that the post-surgical cardiac fibrosis or any other fibrosis mentioned by Spinale is necessarily a CDA1-mediated fibrosis. The burden of proof falls on the PTO in first instance to establish that the fibrosis referred to by Spinale is indeed mediated by CDA-1. Applicants submit that there is nothing to suggest that the level of CDA1 is being modulated in the fibrosis described by Spinale. Indeed, the passage cited above makes it clear that multiple pathways are involved in the generation of fibrosis, and different factors are required to modulate those pathways. Therefore, it cannot be argued that on the balance of probabilities the pathway described by Spinale involved CDA1. As noted above, the Chai Declaration supports applicants' position.

For these reasons, the rejection of claims 10-16 and 21 as anticipated by Spinale should be withdrawn.

The rejection of claims 10-16 and 21 under 35 U.S.C. 102(e) for anticipation by U.S. Patent No. 7,214,375 to Border et al. ("Border"), as evidenced by Ozbun et al., "Identification of Differentially Expressed Nucleolar TGF-beta1 Target (DENTT) in Human Lung Cancer Cells that is a New Member of the TSPY/SET/NAP-1 Superfamily," *Genomics* 73:179-93 (2001) ("Ozbun") and the specification on page 8, lines 30-31 and page 12, lines 32-33 is respectfully traversed.

A significant difference between claim 10 as presented and Border is the use of an AT1 receptor antagonist. There is no express disclosure or suggestion in Border that an AT1 receptor antagonist be used in a method for treatment. Instead, Border teaches the use of agents capable of binding to TGF-beta (such as anti-TGF-beta antibodies), as evidenced by the passage at column 4 (from line 23) which states: "The invention provides a method of inhibiting the accumulation of extracellular matrix in a tissue by suppressing the activity of TGF-beta in the tissue."

Applicants submit that an agent that is capable of suppressing the activity of TGF-beta, clearly does not fall within the scope of the term "AT1 receptor antagonist", as required by amended claim 10. On that basis, alone, pending claim 10 is novel over Border. Furthermore, the PTO has not provided any technical reasoning or evidence that the fibrosis

described by Border is likely to be CDA1-mediated. While Ozbun and the present specification disclose involvement of TGF-beta and CDA1, Ozbun fails to teach that there is a causal connection between the modulation of CDA1 levels and the synthesis of extracellular matrix proteins. Accordingly, it cannot be fairly presumed that the prior art method would be useful in treating a CDA1-mediated fibrotic condition.

In addition to the foregoing, applicants submit that there is no suggestion that fibrosis of the kidney, as a result of diabetes, is the condition treated in Border. The only discussion regarding diabetes is at column 4, lines 47-50 where it is stated: "An increase in the quantity of mesangial matrix … is the earliest histological finding in many forms of glomerulonephritis and in diabetic nephropathy."

The applicants do not dispute that an increase in extracellular matrix protein is a useful marker in the diagnosis of diabetic nephropathy. However, applicants dispute that this can be interpreted as any disclosure or teaching toward the use of any agent described by Border for the treatment of kidney fibrosis as a result of diabetes.

For all these reasons, the rejection of claims 10-16 and 21 for anticipation by Border should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: April 16, 2009

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Exhibit 1: CDA1 Clustal alignment

Exhibit 1 cont.

```
CLUSTAL 2.0.10 multiple sequence alignment

Sequence format is Pearson
Sequence 1: Human_seq    693 aa
Sequence 2: Macaca_seq   696 aa
Sequence 3: Canis_seq    712 aa
Sequence 4: Cattle_seq   709 aa
Sequence 5: Horse_seq    720 aa
Sequence 6: Rat_seq      636 aa
Sequence 7: Mouse_seq    677 aa

 comparing
paramArg[setSeqNoRange]= off
 comparing
 Start of Pairwise alignments
Aligning...

Sequences (1:2) Aligned. Score:  93
Sequences (1:3) Aligned. Score:  75
Sequences (1:4) Aligned. Score:  74
Sequences (1:5) Aligned. Score:  73
Sequences (1:6) Aligned. Score:  68
Sequences (1:7) Aligned. Score:  69
Sequences (2:3) Aligned. Score:  73
Sequences (2:4) Aligned. Score:  70
Sequences (2:5) Aligned. Score:  69
Sequences (2:6) Aligned. Score:  66
Sequences (2:7) Aligned. Score:  65
Sequences (3:4) Aligned. Score:  81
Sequences (3:5) Aligned. Score:  80
Sequences (3:6) Aligned. Score:  67
Sequences (3:7) Aligned. Score:  69
Sequences (4:5) Aligned. Score:  78
Sequences (4:6) Aligned. Score:  68
Sequences (4:7) Aligned. Score:  68
Sequences (5:6) Aligned. Score:  62
Sequences (5:7) Aligned. Score:  63
Sequences (6:7) Aligned. Score:  89
Guide tree file created:   [/ebi/extserv/clustalw-
work/interactive/2009041621/clustalw2-20090416-2130342145.dnd]

There are 6 groups
Start of Multiple Alignment

Aligning...
Group 1: Sequences:   2      Score:14544
Group 2: Sequences:   2      Score:13949
Group 3: Sequences:   3      Score:13683
Group 4: Sequences:   5      Score:12462
Group 5: Sequences:   2      Score:12953
Group 6: Sequences:   7      Score:11269
Alignment Score 63332

CLUSTAL-Alignment file created  [/ebi/extserv/clustalw-
work/interactive/2009041621/clustalw2-20090416-2130342145.aln]
```

Exhibit 1 cont.

```
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Macaca_seq      MDRPDEGPPAKTRRLSSSESPQ------RDPPPPPPPPPLLRLPLPPPQQRPRLQEETEA 54
Canis_seq       MDRQDEGPPAKARRLSSSEPTQ---LDQLPPPPPPPPPLLRLPLPPPEQRPRLREETEA 57
Horse_seq       MGNRTP-PLPKAWN--------------------PQRAALRLPLPPPQQRPRLREETEA 38
Cattle_seq      MDRADEGPPAKARRLSGSEPPQSELLLPPPPPPPPPPPLLRLPLPPPQQRPRLQEETEA 60
Rat_seq         MDRPDEGPPAKTPRLSSSESRQ-------RDLPPPPPPPLLRLPLPPPQQRPRPQEETEA 53
Mouse_seq       MDRPDEGPPAKTPRLSSSEPRQ-------RDLPPPPPPPLQRLPLPPPQQRPRPQEETEA 53
                *..    * .*: .                      *  .  *******:**** :*****

Human_seq       AQVLADMRGVGLGPALPPPPPYVILEEGGIRAYFTLGAECPGWDSTIESGYGEAPPPTES 114
Macaca_seq      AQVLADMRGVGLGPALPPPPPYVILEEGGVRAYFTLGAECPGWDSTIESGYGEAPPPTES 114
Canis_seq       AQVLADMRGVGLGPTLPPPPPYVILEEGGIRAYFTLGAGGPGWEPAMESGYGEAPPPTES 117
Horse_seq       AQVLVDMRGVGLGPTLPPPPPYVILEEGGIRAYFTLGTGGPGWEPGIESGYGEAPPPTES 98
Cattle_seq      AQVLADMRGVGLGPALPPPPPYVILEEGGIRAYFTLGAGGPGWEPAVESGYGESPPLAES 120
Rat_seq         AQVLADMR--GVGPTLPPPLPYVILEEGGIRAYFTLGAESPGWDPAIESGFGEVP-STEI 110
Mouse_seq       AQVLADMR--GVGPTLPPPLPYVILEEGGIRAYFTLSAESPGWDHAMESGFGEAP-STGI 110
                ****.***  *:**:**** *********:******.:  ***:  :***:** *  :

Human_seq       LEALPTPEASGGSLEIDFQVVQSSSFGGEGALETCSAVGWAPQRLVDPKSKEEAIIIVED 174
Macaca_seq      LEALPTPEVSGGSLEIDFEVVQPSSFGGEGALETCSAVGWGPQRLIDPKSKEEAIIIVED 174
Canis_seq       LETFSPSEASGGSLEIDFQVMEPSSFAGEKALETCSAEEWEYQGLAGPRGKEEAIILVED 177
Horse_seq       LEALSPSEAFGGSLGIDFQVMEPSSFAGEKALETCSAEGRGYQRLAGPKGKEEAVIIVED 158
Cattle_seq      LETLSPSEVSGESLEIDFQVTEPSSFAGEKALETCSAGGRGYQRLAGPRGREETVIIVED 180
Rat_seq         IETLPSSEASRGSLEIDFQVAEHSSLG-EKALETCSFGGWGPQMLVGPKRKEEAIIIVED 169
Mouse_seq       METLPSSEISGGSLAIDFQVAEPSSLG-EKALETCSLGGWGPQMLVGPKRKEEAIIIVED 169
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Human_seq       EDEDERESMRS----SRRRRRRRRRKQRKVKRESRERNAERMESILQALEDIQLDLEAVN 230
Macaca_seq      EDEDEQESMRS----SRRRRRRRRRKQRKVKRESRQRNAERMESILQALEDIQLDLEAVN 230
Canis_seq       DDEDEKESVR-------KRRRR-RRK-RKQRKVKKERNAEKIECILQALENIQLDLEAVN 228
Horse_seq       DDEDEKESVR-------KRRRK-KRKQRKVKKESKENNAEKIDYILQALENIQLDLEAVN 210
Cattle_seq      DDEDEKESVR-------KRRRRRKRKPRKVKRESPEKNAEKIECILQALENIQLDLEAVN 233
Rat_seq         EDEDEKESMRRLQQRRRRRRRRRRKQRKAK-ESRERSAQRMESILQALESIQMDLEAVN 228
Mouse_seq       EDEDDKESVR-----RRQRRRRRRRKQRKAK-ESRERSAQRMESILQALESIQMDLEAVN 223
                :***::**:*       :***: :** ** :  . :..*:::: ******.**:******

Human_seq       IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAFLNHPRISILINRRDEDIFRY 290
Macaca_seq      IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAKKHSIKKRITDDKKEEDRFHH 290
Canis_seq       IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAFLNHPKISILINQRDEDIFRY 288
Horse_seq       IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAFFNHPKISILINQRDEDIFRY 270
Cattle_seq      IKAGKAFLRLKRKFIQMRRPFLERRDLIIQNIPGFWVKAFLNHPKISILINQRDEDIFRY 293
Rat_seq         IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAFLNHPRISILINQRDEDIFRY 288
Mouse_seq       IKAGKAFLRLKRKFIQMRRPFLERRDLIIQHIPGFWVKAFLNHPRISILINQRDRDIFRY 283
                ********************************:********  :  :  *  ::::.* *::

Human_seq       LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 349
Macaca_seq      HPHLEQVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 350
Canis_seq       LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 347
Horse_seq       LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 329
Cattle_seq      LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 352
Rat_seq         LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 347
Mouse_seq       LTNL-QVQDLRHISMGYKMKLYFQTNPYFTNMVIVKEFQRNRSGRLVSHSTPIRWHRGQE 342
                 .:* ******************************************************

Human_seq       PQARRHGNQDASHSFFSWFSNHSLPEADRIAEI--IKNDLWVNPLRYYLR-ERGSRIKRK 406
Macaca_seq      PQARRHGNQDASHSFFSWFSNHSLPEADRIAEI--IKNDLWVNPLRYYLR-ERGSRIKRK 407
Canis_seq       PQARRHRNQDTNHSFFSWFSNHSLPEADRIAEI--IKNDLWVNPLRYYMMGEGGYRANRK 405
Horse_seq       PQAHRHRNQDTSHSFFSWFSKHSLPEADRIAEVGPLPNDLWVNPLRYYMMGEGGYRANRK 389
Cattle_seq      PRAHRHGNQDANHSFFSWFSNHSLPEADRIAEI--IKNDLWVNPVRYYMMGEGGYRTSRK 410
Rat_seq         PQVYNRRSHDTRESFFNWFSNHSLPEADRIAEI--IKNDLWVNPVRYYMR-GGGYRTSRK 404
Mouse_seq       PQAYNRRSHDTRESFFNWFSNHSLPEADRIAEI--IKNDLWVNPVRYYMR-RGGYRSSRK 399
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Exhibit 1 cont.

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Human_seq       KQEMKKRKTRGRCEVVIMEDAPDYYAVEDIFSEISDID-----ETIHDIKISDFMETTDY 461
Macaca_seq      KQEMKKRKTRGRCEVVIMEDAPDYYAVEDIFSEISDID-----ETIHDIKISDFMETTDY 462
Canis_seq       KQEKEESKNRDKCEVVILEDSDDYHVMEDIISETSDSDGITDNETIHDIKISDFMETTDC 465
Horse_seq       KQEKEESKNRDECEVVIVEDSDDYHAMEDIISETSDSDGITDSETIHDIKISDFMETTDC 449
Cattle_seq      KQEKEESKNKDEYEVVIMDDSDDYHIMEDIIGETSDSDGITDNETIHDVKISDFMETTDC 470
Rat_seq         KQLGKESRAKNQYEMVIMEDAHDHYAVEDILSEISEIDEITDNETIHDIKISDFMETTDY 464
Mouse_seq       KQHGKE-RAKNQYEMVIMEDAHDHYAIEDILSDISEIDEITDNETIHDIKISDFMETTDY 458
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Human_seq       FETTDNEITDINENICDSENPDHNEVPNN------ETTDNNESADDHETTDNNESAD--- 512
Macaca_seq      FETTDNEITDINENICDSESPDHDEVRN-------ETTDNNESADDNETTDNNESAD--- 512
Canis_seq       FETTDNEITDISESLCDSESPDHNETTDN------ESPDDSETTDNNESSDDSENTDNSQ 519
Horse_seq       FETTDNEITDISESLCDSESPDHNESPDNETINNSESPDDNETTDNNESTDD-ETTDNNE 508
Cattle_seq      FETTDNEITDISESLCDSECPGHNETTDN-----NESPNDNETTDNNESADDKESTN--- 522
Rat_seq         FETTDNEVTDANENLCDSENPDHSEGS-------------HKITDNKGSIATGPDDNG-- 509
Mouse_seq       FETTDNEVTDANENLCDSENPDHSEGYN------------TKITDNKGSVAANPDDNS-- 504
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Human_seq       ----------DNN-------ENPEDNNKNTDDNEENPNNNEN--------TYGN-NFFKG 546
Macaca_seq      ----------DNN-------ENPEDNNKNADDNKENPDNNKH--------TYGN-NFFNG 546
Canis_seq       SS----ENPDDNN-------ENPEDN---TDDNEENTDDNDE-------NPDGDDENPKG 558
Horse_seq       SADDNNENPDDNNENSNDNSENPEDNNN-TDDNEENTDDSDKNADGDNKNPNGDDENPKG 567
Cattle_seq      ----------DNS-------ENPEDDN--TDENEENPDDNDENAD---ENPNGD-ENPKD 559
Rat_seq         --------------------DKPEEKN--TYDSEDSNSEKAD----------GDNKTLEG 537
Mouse_seq       --------------------DDPEEKN--TYDSEDSNSEKAD----------GDNTTLR- 531
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Human_seq       GFWGSHGNNQDSSDSDNEAD-EASDDEDNDGNEGDNEGSDDDGNEGDNEGSDDDDRDIEY 605
Macaca_seq      GFWGSHGNNQDSSDSDNEAD-EASDDEDNDGNEGDNEGSDDDGNEGDNEGSDDDDRDIEY 605
Canis_seq       DNYGSNGNNQDSSDSDNEGDNEGSDDEDNDGNEGDNEGSDDDGNEGDNEGSDDDDRDIED 618
Horse_seq       GNHGSNGNNQDSSDSDNEGDNEGSDYEDNDGNEGDNEGSDDDGNEGDNEGSDDDDRDIED 627
Cattle_seq      GNQRSNGNNQDSSDSDNEGDNDGSDIEDNDGNEGDNEGSDDDGNEGDNEGSDDDDRDIED 619
Rat_seq         DNQQVT-NIQDSSDSDNGDE--GSDDEDDDGNEGDNEGSDDDD------------RDIKY 582
Mouse_seq       DNQQVT-NIQDSSDSDNGDE--GSDDEDDDGNEGDNEGSDDDDD--DNEGSDDDDRDIRY 586
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Canis_seq       YKNNTDDPDKDQDNSNKQDDYEDEVENISEE-SSVEEE---EEGSEEGEESDNEEGSDEE 674
Horse_seq       YRNNIEHPNTDQDNSNNQDDYEDEVESISEEESSVEEE---EEGSEEGSQQQGED-SDDE 683
Cattle_seq      YENYLEDPDKDHHNNTNQDDYEDEVENISEEESSVEEE---EEGSEEGSE-QGEN--SNE 673
Rat_seq         YKNGFEVFDKALDNRTIQDVYEEEVEIISED--SC--------LCQAASPLW--YSCS-- 628
Mouse_seq       YKNGPEVFDKALDNRTNQNDYEEEVELISED--SVEEE---EETSEEASQLS--EDSYED 639
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Human_seq       EGSEDVWEEGEDSDDSDLEDVLQVPNGWANPGKRGKTG 693
Macaca_seq      EGNEDVWEEGEDSDDSDLEDVLQVPNGWANPGKRGKTG 696
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Horse_seq       EGIE-DSEGGEHSEDSYMEEVLQVQNAWANPGKRGKTG 720
Cattle_seq      EGIE--DDSGEDSEDSDMEKVLQVQNPWAIPGKRGQMG 709
Rat_seq         ------------------PEAPPLSP------------ 636
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